

SEP 20 2000

Novartis Pharmaceuticals Corporation
Attention: Lisa N. Pitt, Pharm.D
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Dr. Pitt:

Please refer to your supplemental new drug application dated September 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Transderm-Nitro (nitroglycerin) Transdermal Therapeutic System.

We acknowledge receipt of your submission dated June 27, 2000 that constituted a complete response to our April 11, 2000 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

A Geriatric Use subsection was added to the PRECAUTIONS section:

Clinical studies of transdermal nitroglycerin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your submission of June 27, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.



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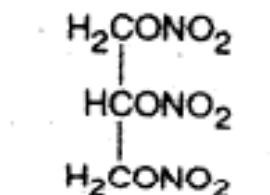
Transderm-Nitro®
nitroglycerin
Transdermal Therapeutic System

Rx only

Prescribing Information

DESCRIPTION

Nitroglycerin is 1, 2, 3-propanetriol, trinitrate, an organic nitrate whose structural formula is



and whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

The Transderm-Nitro (nitroglycerin) transdermal system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin.

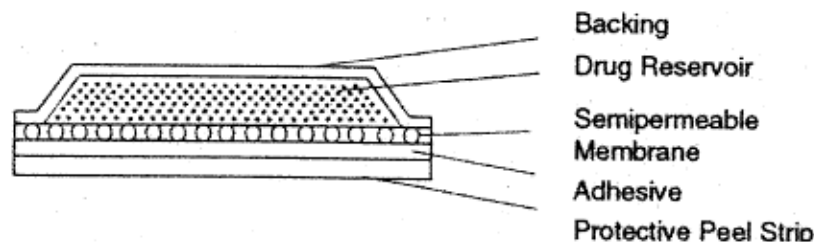
The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each cm² of applied system delivers approximately 0.02 mg of nitroglycerin per hour. Thus, the 5-, 10-, 20-, and 30-cm² systems deliver approximately 0.1, 0.2, 0.4, and 0.6 mg of nitroglycerin per hour, respectively.

The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours,

for example, each system has delivered 10% of its original content of nitroglycerin.

The Transderm-Nitro system comprises four layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid; 3) an ethylene-vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Cross section of the system:



CLINICAL PHARMACOLOGY

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates had been absent from the body for several hours was their antianginal efficacy restored.

Pharmacokinetics

The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow. Known sites of extrahepatic metabolism include red blood cells and vascular walls.

The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1, 2- and 1, 3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin but they are longer-lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known.

The dinitrates are further metabolized to (nonvasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide. To avoid development of tolerance to nitroglycerin, drug-free intervals of 10-12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was less than that exhibited by the parallel group receiving placebo.

In healthy volunteers, steady-state plasma concentrations of

nitroglycerin are reached by about two hours after application of a patch and are maintained for the duration of wearing the system (observations have been limited to 24 hours). Upon removal of the patch, the plasma concentration declines with a half-life of about an hour.

Clinical Trials

Regimens in which nitroglycerin patches were worn for 12 hours daily have been studied in well-controlled trials up to 4 weeks in duration. Starting about 2 hours after application and continuing until 10-12 hours after application, patches that deliver at least 0.4 mg of nitroglycerin per hour have consistently demonstrated greater antianginal activity than placebo. Lower-dose patches have not been as well studied, but in one large, well-controlled trial in which higher-dose patches were also studied, patches delivering 0.2 mg/hr had significantly less antianginal activity than placebo.

It is reasonable to believe that the rate of nitroglycerin absorption from patches may vary with the site of application, but this relationship has not been adequately studied.

The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

INDICATIONS AND USAGE

Transdermal nitroglycerin is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

CONTRAINDICATIONS

Use of Transderm-Nitro (nitroglycerin) transdermal system is contraindicated in patients using Viagra® (sildenafil) because sildenafil may amplify the vasodilatory effects of Transderm-Nitro resulting in severe hypotension.

Allergic reactions to organic nitrates are extremely rare, but

they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS

Amplification of the vasodilatory effects of Transderm-Nitro by sildenafil may result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although

still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients

Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with light-headedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions

The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, impairment of Fertility

Animal carcinogenesis studies with topically applied nitroglycerin have not been performed.

Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was no evidence of mutagenicity in an in vivo dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in in vitro cytogenetic tests in rat and dog tissues.

In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for six months prior to mating of the F₀ generation with treatment continuing through successive F₁ and F₂ generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F₀ generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. In this three-generation study there was no clear

evidence of teratogenicity.

Pregnancy Category C

Animal teratology studies have not been conducted with nitroglycerin transdermal systems. Teratology studies in rats and rabbits; however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of transdermal nitroglycerin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses.

Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see OVERDOSAGE).

Application-site irritation may occur but is rarely severe. In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	6%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE

Hemodynamic Effects

The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope

(especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia

Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b₅ reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively

applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2 . Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

The suggested starting dose is between 0.2 mg/hr*, and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr' have shown continued effectiveness for 10-12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such

when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM

A patient leaflet is supplied with each carton.

HOW SUPPLIED

Nitroglycerin Transdermal System 0.1 mg/hr-tan, round (imprinted Transderm-Nitro 0.1 mg/hr), supplied in a foil-lined pouch

30 Systems . . . NDC 0078-0332-85

Nitroglycerin Transdermal System 0.2 mg/hr-tan, oblong (imprinted Transderm-Nitro 0.2 mg/hr), supplied in a foil-lined pouch

30 Systems NDC 0078-0333-85

Nitroglycerin Transdermal System 0.4 mg/hr-tan, oblong (imprinted Transderm-Nitro 0.4 mg/hr), supplied in a foil-lined pouch

30 Systems NDC 0078-0334-85

Nitroglycerin Transdermal System 0.6 mg/hr-tan, oblong (imprinted Transderm-Nitro 0.6 mg/hr), supplied in a foil-lined pouch

30 Systems NDC 0078-0335-85

*Rated release in vivo. Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied Transderm-Nitro systems would be rated at 2.5 mg/24 hr (0.1 mg/hr), 5 mg/24 hr (0.2 mg/hr), 10 mg/24 hr (0.4 mg/hr), 15 mg/24 hr (0.6 mg/hr), and 20 mg/24 hr (0.8 mg/hr).

Do not store above 30°C (86°F).

Do not store unpouched. Apply immediately upon removal from the pouch.

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